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EU Clinical Trials Regulation 2014: Fetter or facilitator?

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Abstract

European Union (EU) Clinical Trials Regulation 536/2014, expected to come into force in 2019, provides for a streamlined single EU application for cross-border clinical trials and enhanced transparency of results. The status of the Regulation in post-Brexit UK is uncertain. Matters of regulatory alignment will be covered by agreements on the future EU-UK relationship. In the short term, implementation of the Regulation in the United Kingdom depends on the Brexit model and timing of the Regulation's implementation. The EU (Withdrawal) Act will convert EU law into UK law, including the vast array of EU life sciences regulation. However, the Regulation is likely to be implemented after the United Kingdom leaves the EU, but within the transition period. If the United Kingdom is not part of the legal framework governing clinical trials in the EU, then the United Kingdom will still need to comply with the global framework set out in the International Council on Harmonisation if it wants to be part of trials of medicinal products for which marketing authorization will be sought for licensing in the European Economic Area. This article extols the virtues of harmonization with the EU and attempts to counter some of the media focus on the advantages of a deregulated bespoke approach.

Keywords

Clinical trials, Brexit, healthcare research, regulation, life sciences

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Introduction

The Life Sciences sector turns over more than £60 billion per year and employs 220,000 people.¹ In her leadership campaign, Theresa May acknowledged: 'It is hard to think of an industry of greater strategic importance to Britain than its pharmaceutical industry'.²

The Government has confirmed that science and innovation is a Brexit negotiating priority.³ In April 2017, the House of Commons Health Committee identified six health areas where Brexit will have a 'critical effect'.⁴ One of these is health research, and the regulatory procedure for medicinal products was highlighted as an outstanding issue for the successor committee to address.⁵ Given uncertainties in other sectors, the recent Accelerated Access Review warns that 'it seems clear that the life sciences industry will provide a crucial pillar for future economic growth'.⁶ So far, the government has tackled post-Brexit risks to the pharmaceutical industry⁷ with £2 billion per annum of additional investment⁸ a review of Research and Development tax incentives⁹ and an

1. ABPI, *Maintaining and Growing the UK's World Leading Life Sciences Sector in the Context of Leaving the EU*. UK EU Life Sciences Transition Programme Report, for the UK EU Life Sciences Steering Committee, 6 September 2016. Available at: <http://www.abpi.org.uk/our-work/library/industry/Documents/UK-EU-Steering-Group-Report.pdf> (accessed 20 April 2018).
2. Theresa May, Speech, Birmingham, 11 July 2016. Available at: <http://press.conservatives.com/post/147947450370/we-can-make-britain-a-country-that-works-for> (accessed 20 April 2018).
3. HC Hansard Deb 26 January 2017 vol 620 col 12; Dept for Exiting the European Union, *The United Kingdom's Exit From, and New Partnership with, the European Union* Cm 9417, February 2017, section 10. Available at: <https://www.gov.uk/government/publications/the-united-kingdoms-exit-from-and-new-partnership-with-the-european-union-white-paper> (accessed 20 April 2018).
4. Health Committee, *Brexit and Health and Social Care— People & Process*, April 2017, HC 640, para 4. Available at: <https://publications.parliament.uk/pa/cm201617/cmselect/cmhealth/640/640.pdf> (accessed 20 April 2018).
5. Op. cit., para 127.
6. HM Government, *Accelerated Access Review: Final Report*, 2016, p 8. Available at: <https://www.gov.uk/government/publications/accelerated-access-review-final-report> (accessed 20 April 2018). And UK EU Life Sciences Transition Programme Report, *Maintaining and Growing the UK's World Leading Life Sciences Sector in the Context of Leaving the EU*, 2016. Available at: <http://www.abpi.org.uk/our-work/library/industry/Documents/UK-EU-Steering-Group-Report.pdf> (accessed 20 April 2018).
7. A. Gulland, 'How "Brexit" Might Affect the Pharmaceutical Industry', *British Medical Journal* 353 (2016), p. i2615.
8. Autumn Statement 2016. Available at: <https://www.gov.uk/government/topical-events/autumn-statement-2016> (accessed 20 April 2018).
9. HM Government, 'PM Announces Major Research Boost to Make Britain the Go-to Place for Innovators and Investors' 2016', 21 November 2016. Available at: <https://www.gov.uk/government/news/pm-announces-a-2-billion-investment-in-research-and-development> (accessed 20 April 2018).

industrial strategy white paper outlining additional support.¹⁰ But regulatory uncertainties, including those surrounding the clinical trials industry, pose a risk to future development.

This article focuses on the implications of Brexit for clinical trials regulation (CTR) in the United Kingdom. Clinical trials are studies on human participants of the safety and efficacy of medicinal products. Clinical trials are sometimes conducted within a single nation, but larger randomized controlled trials often involve multiple nations. The United Kingdom seeks to attract investment from global biopharmaceutical companies, not least because of the economic advantages this brings but also because of the potential health advantages for research participants and future patients.¹¹

As the clinical trials industry has become increasingly global in nature, national regulations have attempted to balance three potentially competing goals. First, patient safety must be assured through the application of international ethical standards. Second, regulation must be proportionate and efficient or risk disincentivizing industry if research could be conducted more swiftly and economically elsewhere. Third, the data generated must be sufficiently robust to feed into applications for marketing authorization. All medicines must be authorized before marketing, and in the European Union (EU), there are two main routes: The European Medicines Agency (EMA) operates a centralized single marketing authorization or, alternatively, national authorization is possible, in the United Kingdom's case, via the Medicines and Healthcare products Regulatory Agency (MHRA). Recognition by other national authorities of an assessment by a single member state is possible either under the mutual recognition procedure or, where the products have not yet received a marketing authorization, a decentralized procedure.¹²

Though there is a centralized process for marketing authorization, clinical trials of medicinal products must currently be authorized at the national level. EU law on clinical trials is currently governed by the Clinical Trials Directive 2001/20/EC. Each member state was required to enact legislation to implement the Directive, which the United Kingdom achieved via secondary legislation.¹³ While the Directive had a harmonizing impact, it also, as we shall see, increased costly bureaucracy, so damaging the attractiveness of the EU (and the United Kingdom) as a location for cross-border trials.

To address these deficiencies, EU Clinical Trials Regulation 536/2014 was formally adopted by the European Parliament and the Council of the EU in 2014. Though adopted, the CTR will not come into force until 2019. Unlike Directives, Regulations have direct

10. HM Government, *Industrial Strategy: Building a Britain Fit for the Future*, 2017. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/664563/industrial-strategy-white-paper-web-ready-version.pdf (accessed 20 April 2018).

11. Dept for Exiting the European Union, *The United Kingdom's Exit From, and New Partnership with, the European Union* Cm 9417, February 2017, sections 10.12–10.14.

12. See EMA, 'Authorisation of Medicines'. Available at: http://www.ema.europa.eu/ema/index.jsp?%20curl=pages/about_us/general/general_content_000109.jsp&mid=WC0b01ac0580028a47 (accessed 20 April 2018).

13. The Medicines for Human Use (Clinical Trials) Regulations, SI 2004/1031.

applicability and do not require member states to enact national legislation to bring them into force in domestic law. The CTR seeks to make the EU a safe and attractive place to conduct clinical trials, promising to streamline the process for authorizing clinical trials across the EU, improve consistency and transparency and enhance efficiency through tighter deadlines. At the heart of the new regime will be a new Clinical Trials Portal and Database which will serve as a single-entry point for submission of data and information relating to clinical trials required by the CTR. Member states will cooperate in the assessment of proposed trials, and there is provision for each state to individually assess certain issues of an ethical or local nature, such as compensation and certain informed consent requirements. The database and portal will be set up by the EMA. Currently based in London, the EMA will relocate to Amsterdam when the United Kingdom exits the EU.¹⁴

This article raises three questions. How accurate was the pre-referendum debate on clinical trials? What are the advantages of compliance with the CTR? And is compliance legally and politically possible? None of these questions can be answered definitively at this stage, but it is hoped that by posing the questions and outlining potential responses, the advantages of a harmonized approach can counter some of the media portrayals that denigrate EU regulation of clinical trials in favour of a deregulated bespoke approach.

The pre-referendum debate

Inconsistencies in national legislation implementing the EU Clinical Trials Directive 2001 coupled with a risk averse and bureaucratic approach resulted in multiple applications where the research crossed borders, conflicts between ethics committees and a lack of transparency of results. Clinical trials applications in the EU fell by 25% from 2007 to 2011¹⁵ as the EU became decreasingly attractive to scientists.¹⁶ Problems were exacerbated in the United Kingdom due to ‘gold-plating’ the requirements of the Directive in order to better protect research participants, for example, by imposing limitations on emergency research and trials involving vulnerable participants.¹⁷

It will come as little surprise then, that in the run up to the referendum, the maligned Directive was referred to as a reason for leaving the EU. Michael Gove claimed that ‘rules like the EU Clinical Trials Directive have slowed down the creation of new drugs

14. See EMA, ‘Press Release: EMA to Relocate to Amsterdam, the Netherlands’, 20 November 2017. Available at: http://www.ema.europa.eu/ema/index.jsp?%20curl=pages/news_and_events/news/2017/11/news_detail_002857.jsp (accessed 20 April 2018).

15. NHS European Office, ‘The New Clinical Trials Regulation’, 2017. Available at: <http://www.nhsconfed.org/regions-and-eu/nhs-european-office/influencing-eu-policy/clinical-trials> (accessed 20 April 2018).

16. House of Commons Science and Technology Committee, First Report of Session 2016-17, *EU Regulation of the Life Sciences*, HC158, June 2016, Conclusion para 6. Available at: http://www.publications.parliament.uk/pa/cm/cm201617/cmselect/cmsctech/158/15807.htm#_idTextAnchor035 (accessed 20 April 2018).

17. E. Cave, ‘Seen but Not Heard? Children in Clinical Trials’ *Medical Law Review* 18(1) (2010), pp. 1–27.

to cure terrible diseases'.¹⁸ Upon exit from the EU, the United Kingdom would be able to amend the domestic regulations that give the EU Directive force. Visions were presented of Britain as a world leader in healthcare research, finally free of European 'shackles'.¹⁹ Appeals to 'take back control' were reiterated post-referendum.²⁰ There were calls for regulatory reform to make the United Kingdom a global leader in research, limit complexity and cost and to reduce emphasis on the precautionary principle.²¹

Certainly, Brexit brings new opportunities for a distinct approach. Theresa May has promised that post-Brexit: 'Parliament will be free – subject to international agreements and treaties with other countries and the EU on matters such as trade – to amend, repeal and improve any law it chooses'.²² But is a distinct approach desirable? There are at least three potential advantages to amending any inherited regulations on clinical trials: the advancement of medicine, the securement of competitive advantage and the enhancement of the protection and safety of trial participants through a more precautionary approach.

The challenge in research regulation is to achieve a facilitative and proportionate approach that meets the highest ethical standards.²³ While checks and balances in research seem intuitively to be commended, obstacles to research, including unnecessary bureaucracy, deter funders and undermine the health and longevity of future patients. Unnecessary inefficiencies are unethical, but assessments of necessity and proportionality are subjective. Controversy is evident in the array of conflicting international rules, guidelines and standards. Post Brexit, (de)regulation might be utilized to remove obstacles to research in response to economic pressures, reduced EU influence and the legacy of the maligned EU Clinical Trials Directive. There is wide agreement that the conservative and risk averse Directive got it wrong,²⁴ but using the Directive as an argument for

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18. M. Gove, 'EU Referendum: Michael Gove Explains why Britain Should Leave the EU' *The Telegraph* 20 February 2016. Available at: <http://www.telegraph.co.uk/news/newstopics/eureferendum/12166345/European-referendum-Michael-Gove-explains-why-Britain-should-leave-the-EU.html> (accessed 20 April 2018).
 19. A. Dalgleish, 'Brexit Means we can Revive Clinical Trials Killed by the EU' *The Telegraph*, 7 October 2016. Available at: <http://www.telegraph.co.uk/news/2016/10/07/brexit-means-we-can-revive-clinical-trials-killed-by-the-eu/> (accessed 20 April 2018).
 20. J. Stone, 'Slash EU Regulations on Wildlife Protection and Drug Safety Trials after Brexit, Michael Gove Urges' *The Independent* 25 March 2017.
 21. House of Commons Science and Technology Committee, *Leaving the EU: Implications and Opportunities for Science and Research*, HC502, November 2016, paras 49–50. Available at: <https://publications.parliament.uk/pa/cm201617/cmselect/cmsctech/502/502.pdf> (accessed 20 April 2018).
 22. T. May, 'Britain after Brexit: A Vision of a Global Britain' 2 October 2016. Available at: <http://press.conservatives.com/post/151239411635/prime-minister-britain-after-brexit-a-vision-of> (accessed 20 April 2018).
 23. E. Cave and S. Holm, 'New Governance Arrangements for Research Ethics Committees: Is Facilitating Research Achieved at the Cost of Participants' Interest?' *Journal of Medical Ethics* 28 (2001), pp. 318–321.
 24. House of Commons Science and Technology Committee, First Report of Session 2016–17, *EU Regulation of the Life Sciences*, HC158, June 2016, p. 4.

leaving the EU was disingenuous, given its imminent replacement by the new CTR, over which the United Kingdom exercised considerable influence within the EU's legislative process.

The benefits of compliance with the CTR

The CTR addresses many of the deficiencies of the Directive. The United Kingdom took an active role in negotiating the terms of the CTR. Lobbying during draft stages resulted in amendments that met many of industry's concerns.²⁵ The rights, safety, dignity and well-being of research participants remain the priority, but the efficiency, reliability and robustness of the data generated are given enhanced prominence. Let us not forget that the CTR is a response to declining clinical trial numbers and rising costs.²⁶ The Directive's one-size-fits-all approach is replaced by a proportionate regime for low-risk trials, at least where the trial concerns medicinal products that are already authorized or are used off-label with a sufficient evidence base. In addition, the rules on informed consent are reformed,²⁷ with modified approaches applying to cluster trials²⁸ and research where it is difficult to obtain prior consent, such as trials of emergency medicine.²⁹

A minority of commentators argued that the new CTR will not do enough to facilitate research. Writing in the *Telegraph*, Professor Dalgleish, a campaigner for Britain to leave the EU, wasted no remorse on the 'stifling EU world of committees and lobbyists that we are leaving behind' and welcomed a new era in which Britain can 'throw off the shackles of EU regulation in clinical research and fully rejoin the experimentation culture of the anglosphere – and America-led-research'.³⁰ But derogating from the CTR's protections of research participants in order to further facilitate research would exacerbate concerns around participant protection and potentially risk the United Kingdom's reputation on research ethics and integrity. Some commentators have argued that the new CTR already places too much emphasis on facilitation of research, exposing trial subjects to unacceptable levels of risk. Shaw and Townend argue that the simultaneous approval of science and ethics will reduce bureaucracy but hamper ethics committees³¹;

25. E. Zanon 'NHS Confederation Blog. Momentous Changes to EU Rules will Finally Unleash the NHS' Clinical Research Potential' 6 October 2014. Available at: <http://www.nhsconfed.org/blog/2014/10/momentous-changes-to-eu-rules-unleash-nhs-clinical-research-potential> (accessed 20 April 2018).

26. E. Zanon, 'With EU Red Tape Cut, the Shackles are Off Clinical Innovation' *Health Services Journal*, 29 October 2014. Available at: https://www.hsj.co.uk/comment/with-eu-red-tape-cut-the-shackles-are-off-clinical-innovation/5075995.article#.VFD34_nF-1e (accessed 20 April 2018).

27. Articles 28–29.

28. Article 30.

29. Article 35.

30. A. Dalgleish, 'Brexit Means we can Revive Clinical Trials Killed by the EU' *The Telegraph*, 7 October 2016.

31. D. Shaw and D. Townend, 'Division and Discord in the Clinical Trials Regulation' *Journal of Medical Ethics* 42(11) (2016), pp. 729–732.

and Westra fears that assessing risk ‘in comparison with the standard treatment of the subjects’ condition’ raises the potential for exploitation of vulnerable research subjects.³² Where the standard treatment poses significant risk, there is potential to exceed the levels of risk set out in international guidance, such as the Declaration of Helsinki.

Pre-referendum, support for the ‘remain in the EU’ campaign from pharma³³ demonstrated confidence in the CTR, which promised improved cross-border collaboration whereas separation from Europe threatened disruption, inconsistency and reduced funding, partnerships and researcher mobility. The Association of the British Pharmaceutical Industry (ABPI) emphasized the importance of long-term access to European funding and regulatory alignment,³⁴ and the House of Commons Select Committee warned of the need to balance opportunities for reform with the benefits of consistency:

By harmonising the procedures under which research is conducted, EU regulation can foster crossborder collaborations. These multiple state collaborations are evident at least in the conduct of clinical trials, for example, and setting up such trials through a system where permission needed to be sought country by country would likely introduce even more delay and bureaucracy than the current EU system.³⁵

The United Kingdom’s post-Brexit alignment with the CTR would enhance consistency, though Lepola et al. have argued it does not go far enough. As the CTR applies only to investigational medicinal products, a vast array of other healthcare research remains subject to different (national) regulations, paediatric research may be hampered by variation in the legal definition of ‘minor’,³⁶ and there is ostensibly a lack of detail in relation to the regulation of ethics committees and consent/assent requirements which could hamper cross-border trials. If these criticisms are heeded, the result might be an *extension* rather than diminution of the harmonization agenda.

Perhaps, the most persuasive argument for alignment with the CTR is the effect inconsistency might have on marketing authorization. Many trials conducted outside the EU are used in licensing applications for marketing authorization in the European Economic Area (EEA).³⁷ If a trial is to lead to marketing authorization for medicines in

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32. A.W. Westra, ‘Ambiguous Articles in New EU Regulation May Lead to Exploitation of Vulnerable Research subjects’ *Journal of Medical Ethics* 42 (2016), pp. 189–191.
 33. A. Gulland, ‘How “Brexit” Might Affect the Pharmaceutical Industry’ *British Medical Journal* 353 (2016), i2615.
 34. ABPI, *Brexit*. Available at: <http://www.abpi.org.uk/our-work/uk-eu-life-sciences-transition-programme/Pages/default.aspx> (accessed 20 April 2018).
 35. House of Commons Science and Technology Committee, First Report of Session 2016–17, *EU Regulation of the Life Sciences*, HC158, June 2016, para 17 and House of Commons Science and Technology Committee, *Leaving the EU: Implications and Opportunities for Science and Research*, HC502, November 2016, para 50.
 36. P. Lepola, A. Needham, J. Mendum, et al., ‘Informed Consent for Paediatric Clinical Trials in Europe’ *Archives of Disease in Childhood* 101(11) (2016), pp. 1017–1025.
 37. EMA, ‘Clinical Trials Submitted in Marketing-Authorisation Applications to the European Medicines Agency’ 2013. EMA/INS/GCP/676319/2012. Available at: <http://www.ema>.

the EEA, then it must comply with Clinical Directive 2001/20/EC and soon with the CTR. This requires³⁸ that trials conducted outside the EEA must comply with ethical principles ‘equivalent to those set out in the EEA’,³⁹ including the Declaration of Helsinki⁴⁰ and international Good Clinical Practice (GCP). GCP is the international ethical and science quality standard. The EU, Japan and the United States are committed to GCP, which forms the core of the International Council for Harmonisation.⁴¹ Because clinical trials data are included in the application for marketing authorization, the principles developed by the EU extend to any country conducting clinical trials that hope to later market that drug in the EEA.⁴² Derogation from these principles would lead to a limited market at significant cost to the economy.⁴³

Any advantages that might flow from derogating from the CTR must be balanced with the disadvantages posed by inconsistency. Exacerbating the differences between the

europa.eu/ema/index.jsp?%20curl=pages/special_topics/general/general_content_000489.jsp (accessed 20 April 2018).

38. EU Clinical Trials Regulation 536/2014 Article 25(5):

Where the clinical trial referred to in paragraph 4 has been conducted outside the Union, it shall have been conducted in accordance with principles equivalent to those of this Regulation as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial. And see Article 79(1) on Union controls.

39. EMA, ‘Clinical Trials in Human Medicines’. Available at: http://www.ema.europa.eu/ema/index.jsp?%20curl=pages/special_topics/general/general_content_000489.jsp (accessed 20 April 2018).
40. WMA, *Declaration of Helsinki*, 2013. Available at: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/> (accessed 20 April 2018).
41. ICH, *Good Clinical Practice*, December 2016, EMA/CPMP/ICH/135/1995/R2. See M. Flear, *Briefing Paper 2: Brexit and Pharmaceuticals’ Regulation: Optimising the UK’s Post-Brexit Influence in Global Standards-Setting*, October 2017. Available at: <http://www.qub.ac.uk/brexit/Brexitfilestore/Filetoupload,777643,%20en.pdf> (accessed 20 April 2018) on potential implications of Brexit for UK’s role in ICH.
42. EMA, *Reflection Paper on Ethical and GCP Aspects of Clinical Trials of Medicinal Products for Human Use Conducted Outside of the EU/EEA and Submitted in Marketing Authorisation Applications to the EU Regulatory Authorities* 2012. EMA/121340/2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125437.pdf (accessed 20 April 2018).
43. House of Commons Health Committee, *Oral evidence: Brexit – medicines, medical devices and substances of human origin*, HC 392 (23 January 2018), Q389, Dr Williams:
- To get a product to the market, a company would have to go through a separate process for the EU 27, which represents, in terms of the global pharmaceutical market, 23%, and a separate process for the UK market, which represents 3% if we diverged.

Available at: <http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/health-and-social-care-committee/brexit-the-regulation-of-medicines-medical-devices-and-substances-of-human-origin/oral/77523.html> (accessed 20 April 2018).

United Kingdom and the rest of Europe could lead to isolationism.⁴⁴ It is of dubious logic to suggest that we might be free of European ‘shackles’ if doing so will also divest the United Kingdom of marketing potential.

Legal and political barriers

The previous section advanced an argument that there is much to be gained from aligning the United Kingdom’s regulatory position with the CTR. This section asks: How will potential Brexit models affect its implementation? Here it is important to distinguish between the short/medium term and the longer term. Brexit is planned to take place in three stages consisting of withdrawal, transition and a new UK–EU relationship. Even if withdrawal and transition are agreed, a ‘disruptive Brexit’ in which negotiations break down remains possible. In that event, World Trade Organisation law would govern trade with resulting uncertainty for the trade and movement of pharmaceutical and medicinal products in the EU. The Health Committee has expressed concern at the lack of apparent negotiations to prevent disruption to the supply chain in the event of a disruptive Brexit.⁴⁵ There is evidence that one company, GlaxoSmithKline, has already invested £70 million in contingency planning – money that has been diverted from research.⁴⁶

Withdrawal and transition

The Article 50 exit negotiations must be concluded by 30 March 2019, and embodied in a legally binding Withdrawal Agreement, unless the EU27 and the United Kingdom agree to an extension. The United Kingdom has requested an ‘implementation period’, also to be covered by the Withdrawal Agreement, which will take the form of a ‘transition’ that will last from the likely Brexit day on 29 March 2019 to 31 December 2020. In March 2018, a draft Withdrawal Agreement was published.⁴⁷ A Withdrawal Agreement and Implementation Bill will seek to implement the Agreement, financial settlement and transition arrangements.⁴⁸

44. A. Gulland, ‘What Comes Next after Brexit Vote, Scientists Ask’ *British Medical Journal* 353 (2016), i3558.

45. House of Commons Health Committee, *Oral evidence: Brexit – medicines, medical devices and substances of human origin*, HC 392 (23 January 2018), Q337–Q390. An independent analysis from an external consultant has been commissioned: Q340.

46. *Op. cit.*, Q344, Q352.

47. European Commission, European Commission Draft Withdrawal Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community (2018). Available at: https://ec.europa.eu/commission/publications/draft-withdrawal-agreement-withdrawal-united-kingdom-great-britain-and-northern-ireland-european-union-and-european-atomic-energy-community_en (accessed 20 April 2018).

48. Department for Exiting the EU, ‘Press Release: New Bill to Implement Withdrawal Agreement’ 13 November 2017. Available at: <https://www.gov.uk/government/news/new-bill-to-implement-withdrawal-agreement> (accessed 20 April 2018).

Post-referendum, it initially seemed that the United Kingdom would focus on amending existing national legislation based on the Clinical Trials Directive (through the UK Medicines for Human Use (Clinical Trials) Regulations 2004⁴⁹). However, a regulatory black hole has been averted by the announcement of a Great Repeal Bill, officially known as the EU (Withdrawal) Bill.⁵⁰ The Bill repeals the European Communities Act 1972 and brings EU legislation into domestic UK law as a new source of law. Provided agreement is reached on withdrawal, will the CTR become part of ‘retained EU law’ under the (yet to be adopted) EU (Withdrawal) Act? The CTR was adopted, before the referendum vote, in 2014. Nonetheless, it is unlikely that the CTR will be caught by the Bill as it currently stands. While the Bill makes clear the intention to implement EU regulations,⁵¹ it only captures regulations that have ‘effect in EU law immediately before exit day’.⁵² Initially, the aim was for the CTR to be in place by October 2018 with Brexit scheduled to take place by 29 March 2019 (unless an extension is agreed). David Davis, the Brexit Secretary, assumed that the CTR would be captured by the EU (Withdrawal) Act⁵³ and that thereafter revision will be possible:

The UK successfully applied sustained pressure to reform the current [Clinical Trials] directive in the best interests of patients and business. We will follow the EU rules until the point of exit, and those new rules will come into effect shortly. The Great Repeal Bill will convert EU law as it applies, including EU regulations, into domestic law on exit. If needs be, we can reform the regulations after that.⁵⁴

Alas, in its June meeting, the EMA Management Board announced that the application of the CTR was postponed due to technical difficulties with the IT systems that will underpin the portal and database.⁵⁵ The CTR will now be implemented ‘in the second half of 2019’⁵⁶ and is therefore unlikely to be implemented (and thus incorporated into UK law) in time for the likely Brexit day.

From the EMA’s perspective, the expectation at the time of writing is that the United Kingdom becomes a ‘third country’ on 30 March 2019,⁵⁷ though negotiation may lead to

49. SI 2004/1031.

50. EU (Withdrawal) Bill 2017-19, HC Bill 5.

51. Op. cit., Clause 3(2)(a).

52. Op. cit., Clause 3(3).

53. Op. cit.

54. HC Hansard Deb 26 January 2017, vol 620, col 12.

55. EMA, ‘EMA Management Board: Highlights of June 2017 Meeting’ 16 June 2017. Available at: http://www.ema.europa.eu/ema/index.jsp?%20curl=pages/news_and_events/news/2017/06/news_detail_002764.jsp&mid=WC0b01ac058004d5c1 (accessed 20 April 2018).

56. EMA, ‘Clinical Trials Regulation’. Available at: http://www.ema.europa.eu/ema/index.jsp?%20curl=pages/regulation/general/general_content_000629.jsp (accessed 20 April 2018).

57. European Commission, EMA *Notice to Marketing Authorisation Holders of Centrally Authorised Medicinal Products for Human and Veterinary Use* May 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500226603.

extended cooperation during transition.⁵⁸ The transition period, referred to in the draft Withdrawal Agreement, will require continued application of existing and new EU laws, subject to certain exceptions and consultation expectations.⁵⁹ Assuming adherence to the proposed timetable, the CTR would be implemented during the transition period. The likelihood then is that the CTR would be one of the EU laws with which the United Kingdom is required to comply. However, the mechanism by which it will be given effect in domestic law post-transition is currently unclear. It is likely to be achieved via the promised Withdrawal Agreement and Implementation Bill and potentially through the amendment of the EU (Withdrawal) Bill.⁶⁰ If the CTR implementation timetable should slip beyond the transition period, then specific regulation will be required to bring it into UK law.

In April 2018, uncertainty around the application of the CTR in UK law led to a proposed amendment to clause 3 of the EU (Withdrawal) Bill to state: ‘For the purposes of this section, the Clinical Trials Regulation (2014/536) is deemed to be operative immediately before exit day, and therefore it forms part of retained EU law’.⁶¹ The clause elicited the following response from Baroness Goldie:

I can provide noble Lords with the strongest possible reassurance on the UK’s commitment to implement the CTR. If the CTR comes into force during the implementation period, as it is currently expected to do in March 2020, it will apply to the UK. If this opportunity does not come to pass, the Government will seek to bring into UK law all relevant parts of the EU regulation that are within the UK’s control.⁶²

In light of government commitment to bring into UK law those parts of the CTR under UK control, the amendment was withdrawn.

EU-UK relationship

Assuming a Withdrawal Agreement, then after the transition period, the question of the EU-UK relationship(s) arises. These must be negotiated with the EU under different procedures to that pertaining to the Withdrawal Agreement. Trade relationships will be negotiated in accordance with Article 207 of the Treaty on the Functioning of the EU.

pdf (accessed 20 April 2018); European Commission, EMA, *Questions and Answers Related to the United Kingdom’s Withdrawal from the European Union with Regard to the Medicinal Products for Human and Veterinary use within the Framework of the Centralised Procedure*, Rev 01, December 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228739.pdf (accessed 20 April 2018).

58. House of Commons Health Committee, *Oral evidence: Brexit – medicines, medical devices and substances of human origin*, HC 392 (23 January 2018), Q374.

59. Article 122.

60. Hansard Society Blog, ‘Fitting a Transition / Implementation Period into the Process of Legislating for Brexit’. Available at: <https://www.hansardsociety.org.uk/blog/fitting-a-transition-implementation-period-into-the-process-of-legislating> (accessed 20 April 2018).

61. HL Hansard Deb 18 April 2018, vol 790, cols 1214.

62. Ibid, col 1215.

Various models have been mooted. If (like Norway) the United Kingdom remains in the EEA, then the United Kingdom would remain committed to freedoms of goods, persons, services and capital. Change would be minimalized. In the event of a ‘harder’ Brexit,⁶³ the United Kingdom might still (like Switzerland) retain limited access to the single market via a series of bilateral agreements, though the EU has so far proved resistant to such an approach. The United Kingdom could trade with the EU, but would not automatically be subject to EU legislation that goes beyond compliance with single market rules (e.g. on free movement of goods and persons). Breach of the agreements on the Switzerland model would lead to severe penalties, and there is concern that adopting a similar model would not give the United Kingdom sufficient control. Canada’s free-trade deal with the EU imposes more limited obligations but is less comprehensive. A bespoke model capturing Norway’s beneficial access and Canada’s limited obligations may be too much to hope for, given the EU’s stated negotiating position to the effect that an ‘out-but-in’ Brexit would be allowing Britain to ‘have cake and eat it’.⁶⁴

All EU member states are part of the EMA, and EEA countries access the EMA’s centralized marketing authorization procedures but lack a decision-making role. There is hope that the United Kingdom will retain access to EMA processes, but this potential and the precise form access would take, is subject to negotiation.⁶⁵ Current indications signal a more distant relationship with the EMA, which issued a notice in 2017 preparing for the consequences of the United Kingdom’s withdrawal.⁶⁶ The Secretary of State for Health has reportedly said: ‘I do not expect us to remain within the European Medicines Agency, but I am very hopeful that we will continue to work very closely with the EMA’.⁶⁷

63. Dept for Exiting the EU, *White Paper: Legislating for the United Kingdom’s Withdrawal from the European Union*, Cm 9446 March 2017. Available at: <https://www.gov.uk/government/publications/the-repeal-bill-white-paper/legislating-for-the-united-kingdoms-withdrawal-from-the-european-union> (accessed 20 April 2018).

64. See O. Quick, ‘UK Can’t Have Customs Cake and Eat it After Brexit, Says Michel Barnier’ *The Times* (6 February 2018). Available at: <https://www.thetimes.co.uk/article/uk-can-t-have-brex-it-customs-cake-and-eat-it-says-barnier-2l9xm0zlg> (accessed 20 April 2018).

65. House of Commons Health Committee, *Oral evidence: Brexit – medicines, medical devices and substances of human origin*, HC 392 (23 January 2018), Q388.

66. European Commission, *EMA Notice to Marketing Authorisation Holders of Centrally Authorised Medicinal Products for Human and Veterinary Use* May 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500226603.pdf (accessed 20 April 2018); European Commission, EMA, *Questions and Answers Related to the United Kingdom’s Withdrawal from the European Union with Regard to the Medicinal Products for Human and Veterinary use within the Framework of the Centralised Procedure*, Rev 01, December 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228739.pdf (accessed 20 April 2018).

67. Health Committee, *Brexit and Health and Social Care— People & Process*, April 2017, HC 640, chapter 5, para 127. But see HC Hansard Deb 26 January 2017 Col 439 suggesting uncertainty on the government’s position on membership of the EMA.

Models exist for collaboration between the EMA and Switzerland, the United States and Canada, which may provide a basis for the United Kingdom's future relationship.⁶⁸ In March 2018, Theresa May stated her intention to 'explore with the EU, the terms on which the UK could remain part of EU agencies such as . . . the EMA'.⁶⁹ Associate membership would, May recognized, involve a financial contribution and adherence to EMA rules. It is, she said 'the only way to meet our objective of ensuring that these products only need to undergo one series of approvals, in one country' and would ensure continued investment in UK biopharmaceuticals. May emphasized the potential for mutual EU benefit given the expertise of the UK's universities, and the experience of the UK regulator, the MHRA which currently deals with authorizations for products that will be licensed in the United Kingdom.

The EMA currently subcontracts around 30% of its work to the MHRA. In April 2018, the EMA set out plans to redistribute the United Kingdom's portfolio of centrally authorized products at post-authorization stage.⁷⁰ This signals a readiness for separation and a reluctance to postpone action until negotiations are concluded. However, it does not rule out an aligned licensing process that may be created by expanding the remit of the MHRA. A Trade Agreement embodying mutual recognition would facilitate alignment and stability. But the United Kingdom would lose significant influence in the development of future regulations and standards.

A more arms-length relationship with the EMA could allow the United Kingdom wide freedoms to adapt and amend EU laws transferred into UK law via the EU (Withdrawal) Act. It could bring opportunities, such as the ability to respond swiftly to the development of new technologies.⁷¹ The United Kingdom might seek closer alignment with the US Food and Drug Administration, but it has been argued that this would be 'time-consuming and costly'.⁷² Alternatively, an entirely bespoke system is possible, but the complexity of such a task makes it highly unlikely in the short term.⁷³ Misalignment with the EMA carries risks of added bureaucracy, delay and costs to market access.⁷⁴ A

68. See S. Barber, *House of Commons Briefing Paper 8148: Brexit and Medicines Regulation*, November 2017, p. 3. Available at: <http://researchbriefings.files.parliament.uk/documents/CBP-8148/CBP-8148.pdf> (accessed 20 April 2018).

69. Prime Minister's Office, 'PM Speech on our Future Economic Partnership with the European Union' 2 March 2018. Available at: <https://www.gov.uk/government/speeches/pm-speech-on-our-future-economic-partnership-with-the-european-union> (accessed 20 April 2018).

70. EMA, *Redistribution of the UK Centrally Authorised Product Portfolio* EMA/17176/2018, (11 April 2018). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2018/04/WC500247359.pdf (accessed 20 April 2018).

71. See M. Dayan, The Nuffield Trust, *How will our Future Relationship with the EU Shape the NHS?*, 7 November 2017. Available at: <https://www.nuffieldtrust.org.uk/research/brexit-relationship-eu-shape-nhs#overview> (accessed 20 April 2018).

72. House of Lords Select European Union Committee, *Brexit: Trade in Goods*. 16th Report of Session 2016-17, 14 March 2017, HL Paper 129, para 167. Available at: <https://publications.parliament.uk/pa/ld201617/ldselect/ldcom/129/129.pdf> (accessed 20 April 2018).

73. *Ibid.*

74. See H. McKenna, *Five Big Issues for Health and Social Care After the Brexit Vote*, King's Fund, June 2016. Available at: <https://www.kingsfund.org.uk/publications/articles/brexit-and-nhs> (accessed 20 April 2018).

hard Brexit could be disruptive to multicentre trials if separate approvals are required in the EU and United Kingdom. This is particularly so if access is denied to the EMA portal and database. Access is not secured by the United Kingdom's alignment with the CTR but is dependent on negotiations. The government's current advice to pharmaceutical companies is to 'prepare for all scenarios'.⁷⁵ The Scottish Health and Sport Committee heard evidence that the EU's portal was of 'crucial importance'. Shona Robison, Cabinet Secretary for Health and Sport, said: 'Anything short of access to the EU clinical trials portal will be a disaster: we need absolutely to secure that'.⁷⁶ But the EU27 are keen to ensure that the United Kingdom does not secure the advantages of EU membership without the associated burdens.⁷⁷ Access is by no means certain.

Conclusion

There has been an overall decrease in UK employment by global biopharmaceutical companies over the last 10 years,⁷⁸ which the UK government seeks to reverse. Brexit poses a potential threat to this goal and yet, the Brexit vote has not halted investment in the UK clinical trials industry.⁷⁹ In the short-term, the emphasis is on stability. The longer-term picture is harder to predict. The ABPI believes that collaboration and open science will lead to new opportunities post-Brexit. Many of those opportunities flow not from regulatory reform but from developing capacity, capability and sustainability

75. House of Commons Health Committee, *Oral evidence: Brexit – medicines, medical devices and substances of human origin*, HC 392 (23 January 2018), Q370, Q376.

76. Health and Sport Committee, *Impact of leaving the European Union on health and social care in Scotland* Session 5, 20 March 2018. Available at: <http://www.parliament.scot/parliamentarybusiness/report.aspx?%20r=11437&mode=pdf> (accessed 20 April 2018).

77. See O. Quick, 'UK Can't Have Customs Cake and Eat it After Brexit, Says Michel Barnier' *The Times*, (6 February 2018).

78. ABPI, *Open for Innovation: UK Biopharma R&D Sourcebook* 2016, p. 5. Available at: http://www.abpi.org.uk/our-work/library/industry/Documents/Open_for_innovation_ABPI_Sourcebook_2016.pdf (accessed 20 April 2018).

79. 'Pharma Deals are 'Vote of Confidence' Says Government' *BBC News*, 27 November 2017. Available at: <http://www.bbc.co.uk/news/business-42131742> (accessed 20 April 2018); J. Bradshaw, 'Brexit will Create Opportunities for UK, AstraZeneca Chief Says' *The Telegraph* 2 February 2017. Available at: <http://www.telegraph.co.uk/business/2017/02/02/astrazeneca-sales-fall-key-drug-loses-patent-protection/> (accessed 20 April 2018); J. Bradshaw, 'Novo Nordisk sets aside Brexit Fears to Invest £115 m in Oxford Research Centre' *The Telegraph* 30 January 2017. Available at: <http://www.telegraph.co.uk/business/2017/01/30/novo-nordisk-sets-aside-brexit-fears-invest-115m-oxford-research/> (accessed 20 April 2018); C. Cookson, 'Alnylam to Brave Brexit and Set Up European HQ in UK' *Financial Times* 20 September 2016. Available at: <https://www.ft.com/content/9a14af72-7e64-11e6-bc52-0c7211ef3198> (accessed 20 April 2018); BBC News, 'GSK: UK Still 'Attractive' Post Brexit as it Invests £275m' 27 July 2016. Available at: <http://www.bbc.co.uk/news/business-36901027> (accessed 20 April 2018). House of Commons Health Committee, *Oral evidence: Brexit – medicines, medical devices and substances of human origin*, HC 392 (23 January 2018), Q376.

through better integration of the National Health Service into research.⁸⁰ Because these are matters of national competence, Brexit will have no direct effects on those policy and legal changes.

The proclamations in the broadsheets that the United Kingdom will be free of the shackles of European regulation are based on an EU CT Directive that is imminently to be replaced by a new EU CTR. This article has argued that a failure to implement a smooth regulatory transition poses a significant threat to the United Kingdom's ability to maintain and enhance its position in the global clinical trials industry. The United Kingdom's part in the negotiations of the new CTR helped ensure its proportionality and efficiency. A failure to align UK regulation with the CTR, both in the short/medium term and in the longer term, would limit cross-border collaboration and potentially divest the United Kingdom of the many practical advantages of the proportionate regulatory system it encapsulates. The British Medical Association has warned of the dangers of reduced collaboration including delayed access to new medicines caused by increased burden on the MHRA and prioritization by pharmaceutical companies of the more streamlined EEA market, weaker pharmacovigilance and loss of expertise in regulatory processes.⁸¹

The timing of the CTR's implantation may mean that it is not automatically incorporated in the implementation of directly applicable EU law under the (yet to be implemented) EU (Withdrawal) Act. It might still be incorporated through the transition arrangements via the proposed Withdrawal Agreement and Implementation Bill. But the problems do not end with adoption of the CTR. At the time of writing, the United Kingdom's ongoing relationship with the EMA is uncertain. If the United Kingdom is not fully integrated within the EMA, then aligning a new, separate route to authorization via the MHRA would be of benefit to the EU as well as the United Kingdom. The United Kingdom's strong global reputation in the life sciences, the large population, small geographical area and the existence of the NHS and NHS number make the UK an attractive location for multicentre trials and their future inclusion in applications for marketing authorization. Brokering a deal for the United Kingdom to access the Portal and Database would be of mutual benefit. In theory, this could be achieved as part of transition, under the Withdrawal Agreement, but political practice suggests that there is insufficient time to achieve this goal, given the other, highly complex, matters that need to be resolved for the Withdrawal Agreement to be adopted as a binding legal text: The CTR is but one of around 12,000 EU regulations.⁸² An EU-UK Agreement to this effect applicable post-transition would need to be negotiated separately, taking into account the EU's competences to enter into international treaties with 'third countries'.

80. Academy of Medical Sciences and ABPI, *The UK Drug Discovery Landscape*, November 2016, pp. 4–5. Available at: <http://www.abpi.org.uk/our-work/library/Documents/The%20UK%20Drug%20Discovery%20Landscape%20v11.pdf> (accessed 20 April 2018).

81. BMA, *Brexit Briefing: Medicines and medical devices regulation: Maintaining an effective working relationship between the UK and the EU*, 2017. Available at: <http://BMA-brexit-briefing-medical-and-medical-devices-regulation.pdf> (accessed 20 April 2018).

82. Department for Exiting the EU, *White Paper: Legislating for the United Kingdom's Withdrawal from the European Union*, Cm 9446 March 2017, para 2.6.

This article has set out substantive and procedural reasons why alignment with the EU CTR would be advantageous and set out barriers to its execution. There is clear commitment from the government to secure both alignment with the CTR and a strong relationship with the EMA, but so far the EMA has not demonstrably accepted the arguments of mutual benefit. Negotiators face a gargantuan task upon which, it is no exaggeration to say, lives depend.

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